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Adverse Effects of a Single Dose of Gentamicin in Adults: A Systematic Review

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Structured Summary

Aim

Systematically review the frequency and type of adverse events associated with a single dose of intravenous or intramuscular gentamicin in adults, for any indication, in studies where a comparator was available.

Methods

A review protocol was developed and registered (PROSPERO: CRD42013003229). Studies were eligible for review if they; recruited participants ≥16 years old, used gentamicin intramuscularly or intravenously as a single one-off dose, compared gentamicin to another medication or placebo, and if adverse events were monitored. MEDLINE, EMBASE, Cochrane Library, trial registries, conference proceedings and other relevant databases were searched up to November 2016. Risk of bias was assessed on all included studies.

Results

15,522 records were identified. After removal of duplicates, screening of title/abstracts for relevance and independent selection of full texts by two reviewers, 36 studies were included. 24,107 received a single one-off dose of gentamicin (doses ranged from 1mg/kg - 480mg per dose). Acute kidney injury was described in 2520 participants receiving gentamicin. The large majority of cases were reversible. There were no cases of ototoxicity reported in patients receiving gentamicin. A meta-analysis was not performed due to study heterogeneity.

Conclusions

A significant number of patients saw a transient rise in creatinine after a single dose of gentamicin at doses up to 480mg. Persistent renal impairment and other adverse events were relatively rare.

Introduction

Gentamicin is a well-established antibiotic initially discovered in 1963(1) which is particularly useful for treating bacteria resistant to other antimicrobials. It is bactericidal and effective against gram-negative and limited gram-positive organisms. Gentamicin is not metabolised but distributed essentially unchanged within the extracellular space before excretion in the kidneys by glomerular filtration.(2) Its use is limited by potentially serious adverse effects, most commonly ototoxicity and nephrotoxicity.

Gentamicin was previously given as a multi dose regimen each day, modified according to serum drug levels. Several studies have shown that single-daily dosing of gentamicin offers an equal, if not improved, toxicity profile.(3) However, the toxicity profile of a single one off dose of gentamicin, as opposed to multiple doses over several days, remains unclear. A single dose is used as a prophylaxis prior to surgery or invasive procedures, such as endoscopic retrograde cholangio-pancreatography, and has also been proven to be effective in the treatment of gonorrhoea.(4-6) It is possible that a one off dose is less toxic and may have a lower risk of adverse effects. Previous systematic reviews of gentamicin safety have focused on a specific indication for use(7), drug preparation(8), treatment population(9), individual adverse effect(10) or dosing regimen(11), but none have evaluated single dose gentamicin. The aim of this systematic review was to assess the frequency and type of adverse events associated with the use of a single dose of intravenous or intramuscular gentamicin in adults.

Methods

A systematic review protocol was developed and registered with PROSPERO at the Centre for Reviews and Dissemination, University of York (Reg No. CRD42013003229 http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013003229).

Eligibility Criteria

Studies were considered eligible for the review if they fulfilled the following criteria; human participants; male or female; ≥16 years old; intramuscular or intravenous gentamicin as a single one-off dose; control group; adverse effects monitored. The control group could comprise of any of the following; placebo, no treatment or an antimicrobial regimen which did not include gentamicin. By including studies with one of these groups as a control allowed us to better identify the true adverse effects of single dose gentamicin. If a study did not have a control group then it was not included in this review. For this reason case studies, case reviews and some longitudinal studies were excluded based on the study design. No other restriction on study design was applied. There was no restriction on the indication for treatment, dose of gentamicin, length of follow up, clinical setting in which gentamicin was given, year of publication or publication status.

Search strategy

The following electronic databases were searched; The Cochrane Library (including the Health Technology Assessment database), MEDLINE, EMBASE, British Nursing Index and Cumulative Index Nursing and Allied Health Literature (CINAHL). The following were searched specifically for systematic reviews and guidelines: National Guideline Clearinghouse, NICE and SIGN. Ongoing trials were sought through the following trial registers; clinicaltrials.gov, WHO International Clinical Trials Registry Platform (ICTRP) and Current Controlled Trials. Conference abstracts and proceedings were searched using zetoc and Conference Proceedings Citation Index (CPCI), for all years available. Dissertations and theses were searched using ProQuest, Index to Theses in Great Britain and Ireland and EThOS. Specific sources of drug information were searched, including pharmacovigilance data from regulatory authorities (electronic Medicines Compendium

[eMC], US Food and Drug Administration [FDA] and Medicines and Healthcare products Regulatory Agency [MHRA]) and a specific drug bibliographic database (TOXLINE). Citation searching was carried out on included articles. In order to identify grey literature, the National Technical Information Service (NTIS) and OpenGrey were searched. Scoping searches were carried out to refine the search strategy. The initial search was carried out in the first week of February 2013, with an update search carried out in the first week of November 2016. An example of the search strategy used for one large database is available in Online Appendix 1. Where the full search strategy could not be used the word 'gentamicin' and its alternatives were searched for separately.

Study selection

All identified records were entered into Reference Manager Version 11.0 and duplicates removed. Titles and, where available, abstracts were screened by one reviewer for relevance, using the eligibility criteria. Due to the number of records it was not feasible for two independent reviewers to carry out this process but as a check for consistency 10% of records were randomly selected, using a random number generator, and screened independently by a second reviewer. Full text articles were sought for all potentially relevant records. Inclusion and exclusion criteria were applied to all full articles independently by two reviewers. Any disagreement between the two reviewers was resolved by discussion or by a third independent reviewer when necessary. Foreign language records were included when searching, and titles and abstracts were translated to allow screening. All potentially relevant foreign language studies were translated for assessment and, if appropriate, data extraction.

Data extraction

The data extraction form (Online Appendix 2) was designed and piloted on five studies. Data extraction was carried out independently by two reviewers on all included studies. The following study characteristics were collected: 1) author; 2) study design; 3) country of publication; 4) number of participants; 5) age range of participants; 6) gender of participants; 7) dose of gentamicin; and 8) indication for gentamicin. Specific details about adverse events were collected for the gentamicin and control groups including: 1) number of participants 2) frequency of adverse events; 3) type of adverse events; 4) severity of adverse events and 5) length of follow up.

Risk of bias assessment

Risk of bias assessment was included within the data extraction form and was independently assessed by two reviewers. Risk of bias was assessed with a tool specific to the study design. Randomised trials were assessed using 'The Cochrane Collaboration's tool for assessing risk of bias'. Non-randomised trials were assessed using the Newcastle-Ottawa Scale for cohort studies or case control studies, as appropriate. Specific risk of bias assessment for our outcome measure, adverse events, was carried out on all studies. This provided a common risk of bias assessment for all studies. For the risk of bias assessment of adverse events we used questions recommended by the Cochrane Collaboration.(12-14)

Data synthesis

Characteristics, main findings and risk of bias assessment were tabulated for each study. If data were appropriate for meta-analysis, it was planned that results would be presented as a summary risk ratio with 95% confidence intervals, on an intention-to-treat basis.

Variations to Protocol

In our published protocol we planned to include studies comparing single one-off dose of gentamicin to a group receiving gentamicin in conjunction with other antimicrobials. To better identify genuine adverse effects of single dose gentamicin we later modified our protocol and excluded these studies.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (15), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (16).

Results

The searches identified 15,522 records, of which 6,858 were duplicates, leaving 8,664 unique studies. Many of the duplicates were generated when searching TOXLINE database which generates a separate output for each search term (e.g. gentamicin, gentamycin and cidomycin). Due to the number of records, only one reviewer screened all the articles for relevance. A second reviewer screened 10% (n=880) of the records to assess consistency and agreement between reviewers was moderate. When assessing the eligibility of full-text articles we found that some studies recruited both children and adults but none provided separate analysis by age group. Studies where ≥ 80% of participants were <16 years old were excluded. The flow diagram for study selection is shown in Figure 1.

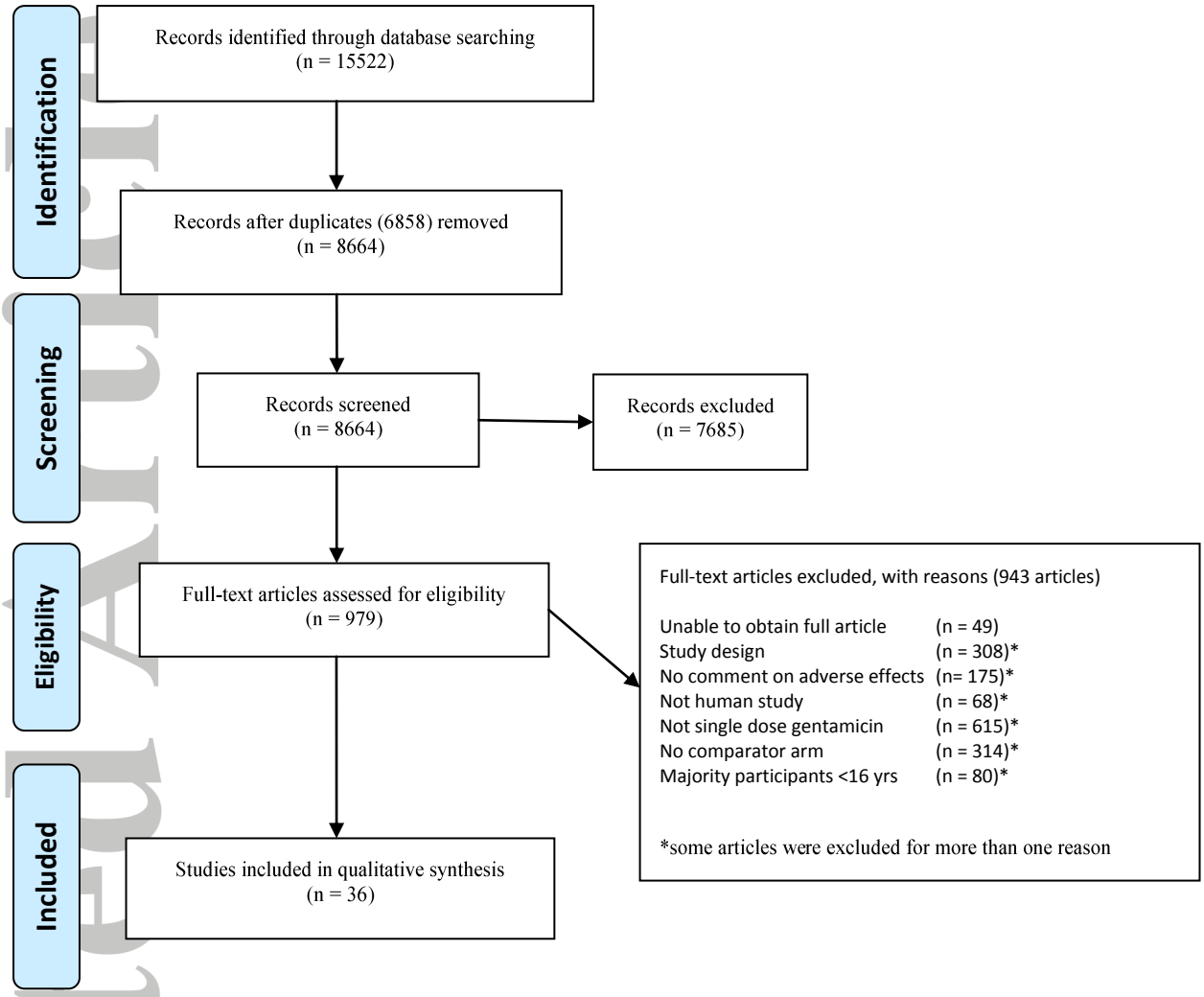


Figure 1: PRISMA Flow Diagram for the Systematic Review of the Adverse Effects of Single Dose Gentamicin in Adults

Characteristics of included studies

36 studies were included in the final synthesis; one thesis (17), and 35 journal articles (5, 18-51). The 36 studies included 11 randomised controlled studies (two crossover designs), 18 cohort studies, one retrospective survey, three pharmacokinetic and three quasi experimental studies. In keeping with our background understanding and scoping searches, no existing systematic review evaluating the safety of single dose gentamicin was identified.

Across all the included studies, 24,107 participants (Male 11,107, Female 11,332)* received a single one-off dose of gentamicin. Ages ranged from 18-95 years old and the dose of gentamicin ranged from 1mg/kg to 480mg. Indications for a single dose of gentamicin included prophylaxis prior to or during surgery (n=20), cystogram (n=1) or transrectal prostate biopsy (n=1). It was also used to treat sepsis (n=1), gonorrhoea (n=3) and urinary tract infections (n=2). Table 1 shows the characteristics of all included studies.

*Data not available for all studies

Table 1: Characteristics of Included Studies

Study (Year of publication)	Design	Country	Total number participants enrolled (those receiving gentamicin)	Age (years) *In format reported*	Gender	Dose and route of Gentamicin	Indication for Gentamicin	Length of follow up
Adelman *et al*(29) (1982)	RCT Crossover	USA	10 (10)	Not available	Not available	1mg/kg/hr IV	Nil, pharmacokinetic study	30 days
Ahmed *et al*(46) (2016)	Cohort	UK	1500 (756)	Mean 81.3	Male = 384 Female = 1116	5mg/kg (max 480mg) IV 2mg/kg renal impairmentIV	Preoperative prophylaxis, hip-fracture patients	30 days
Bailey *et al*(41) (2014)	Cohort	UK	560 (254)	Mean 65.25	Male = 245 Female = 247 Excluded = 68	'Ideal Body Weight' charts* IV	Surgical prophylaxis, elective total hip or knee replacement	23 months
Bell *et al*†(40) (2014)	Cohort	UK	12883 (6655)	Mean 65.46	Data or publication error ǂ	4mg/kg IV	Surgical prophylaxis	1 year
Challagundla *et al*(36) (2013)	Cohort	UK	198 (98)	Range 39-95	Male = 81 Female = 117	160mg (>60kg) IV 120mg (<60kg) IV	Surgical prophylaxis, elective total hip or knee replacement	6 months
Cobussen *et al*(47) (2016)	Cohort	Netherlands	302 (179)	Mean 68	Male = 155 Female = 147	4.7mg/kg +/- 0.7 (SD) IV	Treatment of sepsis in emergency department	28 days
Contrepois *et al*(28) (1985)	RCT Crossover	France	33 (6)	Range 21-28	Male = 33	1mg/kg/hr IV	Nil, pharmacokinetic study	Not available
Craig *et al*(50) (2012)	Matched Cohort	UK	200 (100)	Mean 81.95	Male = 56 Female = 144	240mg IV	Preoperative prophylaxis, hip-fracture patients	7 days
Craxford *et al*(43) (2014)	Cohort	UK	400 (200)	Range 40-91	Not available	3mg/kg IV	Surgical prophylaxis, elective total hip or knee replacement	1 year
Craxford *et al*(42) (2014)	Cohort	UK	180 (90)	Not available	Not available	2mg/kg IV	Prophylaxis, spinal surgery	Not available
Creasey *et al*(33) (1984)	Pharmacokinetic	USA	48 (12)	Range 19-32	Male = 48	80mg IV	Nil, pharmacokinetic study	24hr
Dobbs *et al*(25) (1976)	Quasi experimental Crossover	UK	6 (6)	Range 20-49	Not available	80mg IV	Nil, experimental	1 month
Dubrovskaya *et al*(45) (2015)	Cohort	USA	4177 (1590)	Median 61 (IQR 51-69)	Male = 1659 Female = 2518	Weight based 160mg–400mg IV	Perioperative prophylaxis, orthopaedic surgery	5 days
Fried *et al*(23) (1996)	RCT	USA	142 (72)	Range 19-90	Male = 107 Female = 35	1.5mg/kg IM	Prophylaxis prior to cystometrogram and/or cystogram studies	1-2 weeks
Giri *et al*(34) (2016)	RCT	India	100 (50)	Range 18-80	Male = 49 Female = 51	5mg/kg IV	Surgical prophylaxis	1 month
Hira *et al*(22) (1985)	RCT	Zambia	415 (302)	Not available	Male = 415	280mg IM	Uncomplicated gonococcal urethritis	14 days
Jahre *et al*(32)	Pharmacokinetic	USA	6 (6)	Not available	Not available	1mg/kg IM	Nil, pharmacokinetic study	24hr – 1

* Ideal Body Charts based on height and gender, no further details. † Possible overlap in data. ǂ Gender data is greater than total number of participant

(1978)									month
Jettoo *et al*(35) (2013)	Matched Cohort	UK	220 (107)	Mean 82.5	Male = 52 Female = 168	5mg/kg	IV	Prophylaxis, hip hemiarthroplasty for femoral neck fractures	180 days
Kirkcaldy *et al*(5) (2014)	RCT	USA	614 (305)	Median 26 (IQR 22-35) and 29 (IQR 22-36)	Male = 491 Female = 121 Data missing = 2	240mg(>45kg) or 5mg/kg(<45kg)	IM	Treatment of gonorrhoea	30 days
Kleinschmidt *et al*(24) (1983)	RCT	Germany	65 (34)	Range 18-61	Female = 65	120mg	IM	Treatment of cystitis	4-6 weeks
Lorber *et al*(49) (2013)	Retrospective survey	Israel	1666 (1085)	Mean 63.5	Male = 1666	80mg 160mg 240mg	IM IM IM	Prophylaxis, transrectal prostate biopsy	10 days
McEntee *et al*(26) (1987)	RCT	UK	61 (17)	Not available	Male = 61	80mg IV		Prophylaxis in high risk patients undergoing prostatectomy	Not available
Meyers *et al*(31) (1972)	Pharmacokinetic	USA	20 (7, 3, 6)	Range 22-30	Male = 11 Female = 9	100mg 1mg/kg 1.5mg/kg	IM IV IV	Nil, pharmacokinetic study	8 hours
Mukherjee *et al*(38) (2013)	Cohort	UK	63 (40)	Not available	Male = 48 Female = 15	Not available	IV	Perioperative prophylaxis, radical cystectomy	2 days, unclear if longer
Ndele(17)	Quasi experimental Crossover	Not available	6 (6)	Range 28-45	Male = 6	120mg	IV	Nil, experimental	1 month
Nielson *et al*(37) (2013)	Cohort	Denmark	3461 (1716)	Not available	Not available Excluded = 438	240mg (<120kg) 480mg (≥120kg)	IV IV	Prophylaxis, cardiac surgery	3 days
Nielson *et al*(44) (2014)	Cohort	Denmark	1336 (668)	Range 50-78	Male = 966 Female = 370	240mg (≤120kg) 480mg (>120kg)	IV IV	Preoperative prophylaxis, cardiac surgery	1 year
Pareek *et al*(27) (1981)	Quasi experimental	Saudia Arabia	40 (20)	Not available	Not available	160mg	IM	Treatment of gonorrhoea	Not available
Pons *et al*(21) (1993)	RCT	USA	910 (404)	Not available	Not available	80mg	IV	Preoperative prophylaxis	3 months
Rakovec *et al*(30) (1985)	Cohort	Yugoslavia	1004 (572)	Mean 63.8	Male = 513 Female = 491	80mg	IV	Preoperative prophylaxis, colorectal surgery	Not available
Ross *et al*(51) (2013)	Cohort	UK	281 (149)	Range 53-91	Male = 118 Female = 155 Excluded = 8	4mg/kg	IV	Preoperative prophylaxis, hip and knee arthroplasty	3 or 4 days
Rowlands *et al*(18) (1982)	RCT	UK	129 (67)	Range 18-60+	Not available	120mg	IV	Intraoperative prophylaxis, emergency abdominal surgery	4 weeks
Solgaard *et al*(19) (2000)	Cohort	Denmark	163 (93)	Range 31-101	Male = 37 Female = 126	240mg	IV	Preoperative prophylaxis	7 days
Sprowson *et al*(39) (2013)	Cohort	UK	8195 (2101)	Mean 69.05	Not available	4.5mg/kg	IV	Preoperative prophylaxis, primary joint arthroplasty	30 days

* Ideal Body Charts based on height and gender, no further details. † Possible overlap in data. ǂ Gender data is greater than total number of participant

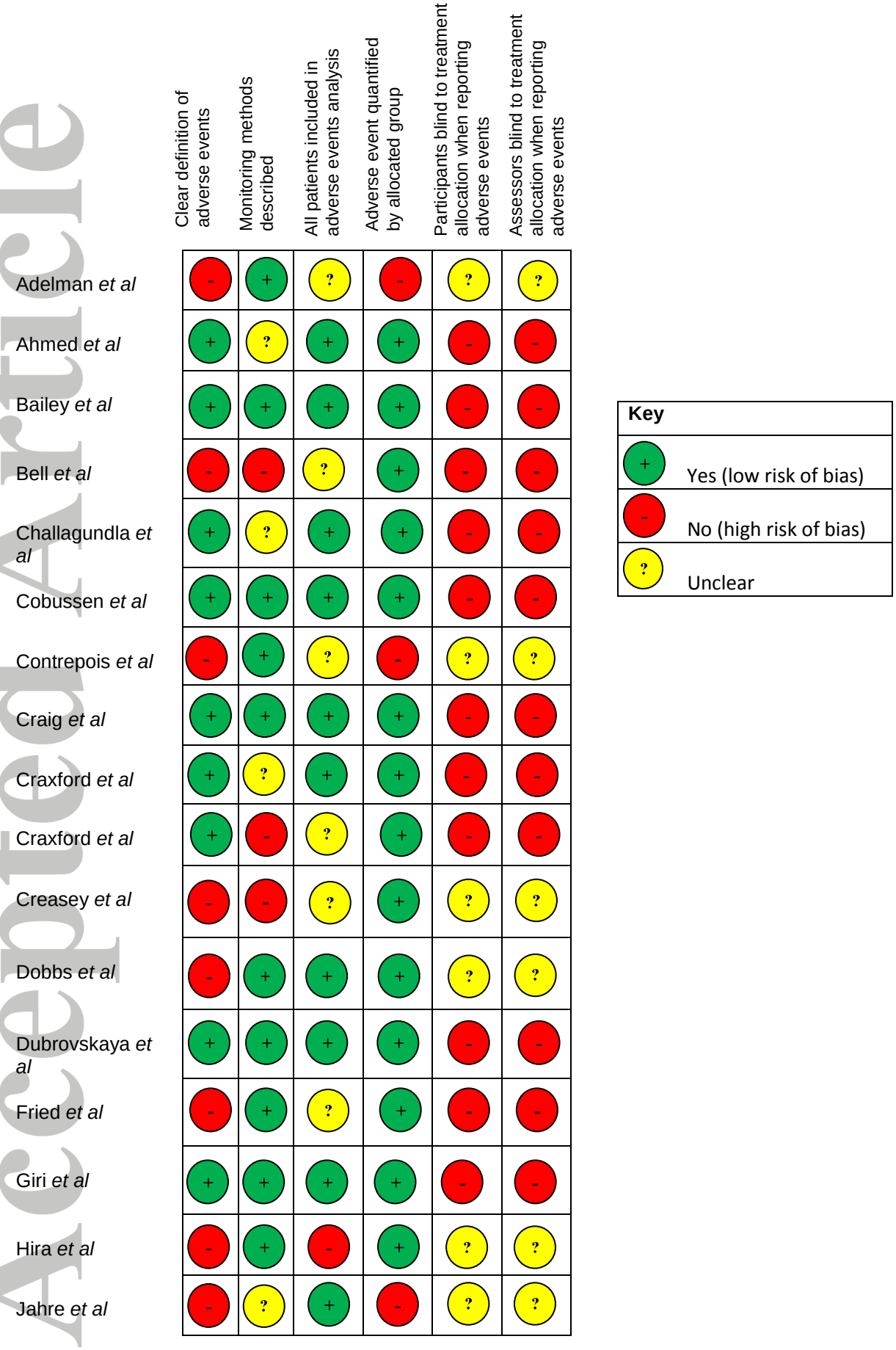
Sundman *et al*(20) (1997)	RCT	Sweden	158 (54)	Range 20-94	Male = 57 Female = 44 Excluded = 57	3mg/kg	IV	Febrile UTI requiring hospitalisation	12-21 days
Walker *et al*†(48) (2016)	Cohort	UK	9242 (6267)	Mean 68.7	Male = 3849 Female = 5393	4mg/kg	IV	Prophylaxis, orthopaedic surgery, excluding NOF repair	1 year

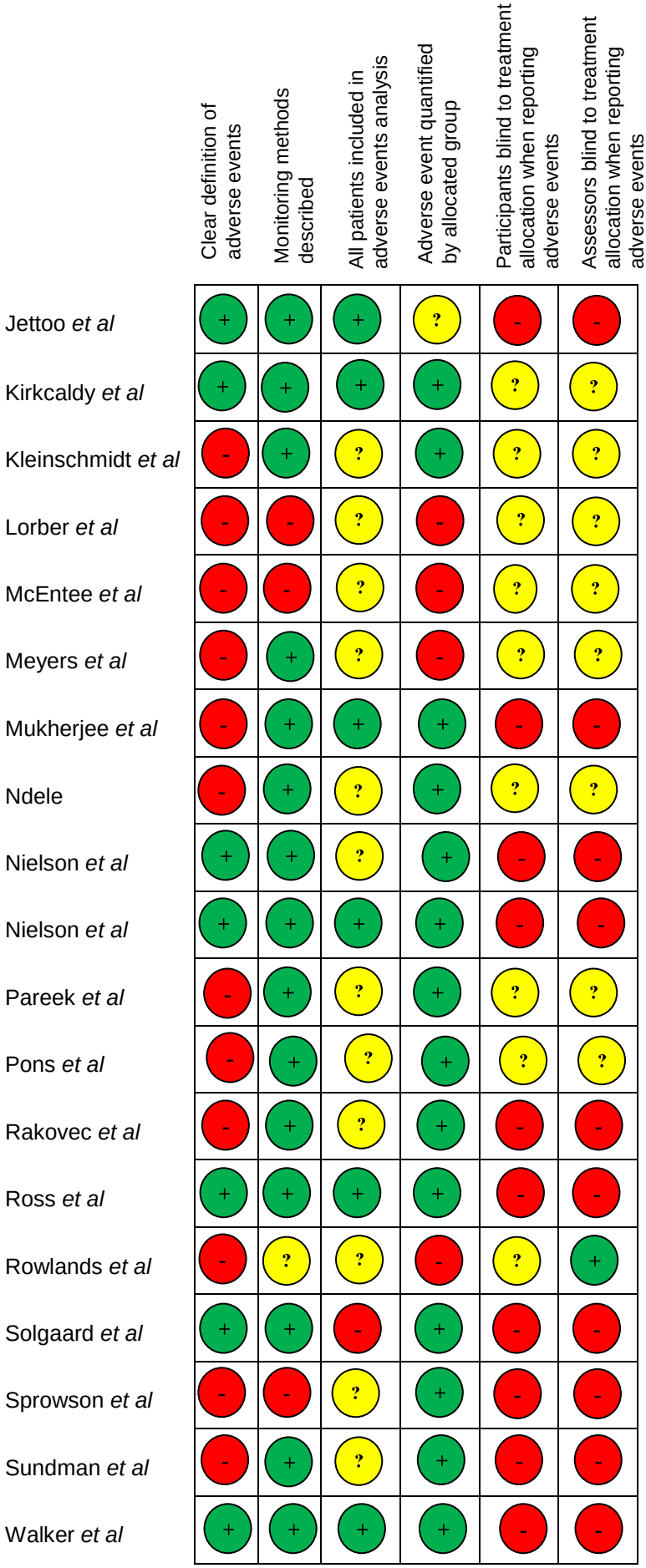
* Ideal Body Charts based on height and gender, no further details. † Possible overlap in data. ǂ Gender data is greater than total number of participant

Risk of bias assessment

The risk of bias for each study is summarised in Figure 2. Monitoring and reporting of adverse events varied greatly between studies. The definition of adverse events was poorly reported, especially for older studies. Information about allocation concealment and blinding at the time of adverse event reporting was not recorded for the majority of studies. Reporting of adverse events frequently lacked detail, making it difficult to assess the risk of bias accurately. However, most studies did provide numerical data on adverse event rates according to intervention group

Figure 2: Risk of bias assessment of included studies





Reported adverse events are summarised in Table 2. Twenty three (5, 19, 21, 23, 30, 33-48, 50, 51), of the 36 included studies, reported adverse events in the gentamicin arm of their study although not all adverse events were related to gentamicin. Pons *et al* (21), the largest randomised controlled trial, had 910 participants who received ceftizoxime, or gentamicin plus vancomycin as antimicrobial prophylaxis prior to neurosurgery. Adverse events were not the primary outcome, but serum creatinine and urea were measured pre and 48hrs post operatively. There were no adverse drug reactions in the ceftizoxime group and six reactions reported in the gentamicin plus vancomycin group. All six reactions were 'significant hypotension and/or flushing', consistent with red man syndrome, a known adverse reaction associated with vancomycin. The first 186 patients enrolled into this study had a 'comprehensive review, urinalysis and serum studies' and 'there was no evidence of haematological, metabolic, hepatic or renal toxicity in either group'. Mean pre-treatment serum creatinine was 79.56 µmol/L in the ceftizoxime group and 76.02 µmol/L in the gentamicin plus vancomycin group. Post-treatment mean creatinine was 73.37 µmol/L and 70.72 µmol/L respectively. Although the paper concludes that ceftizoxime is less toxic than vancomycin plus gentamicin, this seems to be based on the adverse event data associated with vancomycin.

Fried *et al* (23) compared a single dose of gentamicin with an alternative antibiotic regimen (chosen on the basis of urine culture and sensitivity testing three weeks earlier) given as prophylaxis prior to cystometrogram and/or cystogram. The study's main focus was clinical outcome and cost effectiveness. It was quasi-randomised with patients divided into groups based on whether their medical record number ended in an odd or even number. Seventy patients were included in the oral antibiotic group and 72 in the gentamicin group, mostly treated as outpatients. No differences in adverse events were found between the two groups.

This study also asked participants in both groups to rate the 'comfort' and 'convenience' of treatment, on a scale of 1-5 (1=poor and 5=excellent). The gentamicin injection was preferable to oral antibiotics, with a mean convenience score of 4.42 in the gentamicin group compared to 3.63 in the oral antibiotic group and a mean comfort score of 4.24 in the gentamicin group compared to 3.83 in the oral antibiotic group.

Kirkcaldy *et al* (5) was the most recent, large randomised controlled trial assessing single dose gentamicin. Comprehensive monitoring for adverse events was undertaken with a high and equal frequency of adverse events in both arms of the trial. Nausea, vomiting and diarrhoea were the most commonly reported events and were attributed to azithromycin, which was given in both arms of the trial. No serious adverse events were reported over 30 days of follow-up. No specific monitoring for nephrotoxicity or ototoxicity was undertaken.

Creasey *et al* (33) assessed the pharmacokinetic interaction between aztreonam and a number of other antibiotics, including gentamicin. There was one reported side effect in the gentamicin group comprising a transient rise in glutamic pyruvic transaminase, a liver enzyme.

A significant number of studies (34-51) have been published in the last three years, almost as many as in the previous 50 years. The majority of these recent studies are a form of cohort study, without randomisation. Many of the studies reviewed a change in local antibiotic policies, particularly within orthopaedic surgery (35, 36, 39, 41, 43, 45, 46, 48, 50, 51). Authors compared a cephalosporin with gentamicin plus another antibiotic, frequently flucloxacillin. The studies focused on renal impairment with little or no mention of other adverse events. It should be noted that there is a possible overlap of data between studies by

Bell *et al* (40) and Walker *et al* (48). Walker *et al* (48) presented data from NHS Tayside, orthopaedic department between October 2008 and December 2013 which may also be included with the study by Bell *et al* (40) covering five surgical specialities (including orthopaedic surgery) in NHS Tayside between October 2006 and September 2010.

Challagundlla *et al* (36) divided patients into four groups, high dose flucloxacillin plus gentamicin, low dose flucloxacillin plus gentamicin, and two groups receiving cefuroxime (data collected retrospectively and prospectively). The dose of gentamicin was the same in both flucloxacillin groups. The study found the 'peak incidence of Acute Kidney Injury (AKI) clearly coincides with the use of high dose flucloxacillin with single dose gentamicin'. Six of seven cases of renal failure (RIFLE Class F) (52) occurred in the high dose flucloxacillin group compared with one in the low dose flucloxacillin group.

Seventeen (19, 30, 34, 37-48, 50, 51) studies reported nephrotoxicity following gentamicin. A definition of nephrotoxicity or AKI was often absent or varied between studies (Figure 2). Where available the definition used by a particular study has been provided.

Rakovec *et al* (30) included 1004 participants given either a single dose of gentamicin plus metronidazole or no antibiotics, prior to colorectal surgery. A large number of participants, 749, had a diagnosis of carcinoma and 255 had 'other diseases' which were not specified. Blood tests were used to monitor adverse events and a total of 38 events were reported. Nineteen patients had a transient rise in creatinine level, 13 patients had a short-lived increase in Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT), two patients had eosinophilia and four exhibited an exanthema. We

have assumed that these adverse effects were seen in the antibiotic prophylaxis group, although this was not made explicit in the published article.

Solgaard *et al* (19), a cohort study, compared dicloxacillin plus gentamicin to placebo as pre-operative prophylaxis in patients with intertrochanteric hip fractures. This study recruited 163 patients, up to 101 years old and excluded those with a pre-operative creatinine >121µmol/L. The study focused on nephrotoxicity, providing a clear definition of reversible and irreversible nephrotoxicity and description of how renal function was monitored. The group that received gentamicin had a median rise in creatinine, 17.2 µmol/L. This was significantly greater than the placebo group, which saw no rise in creatinine. However, at day seven post-op no significant difference was seen in creatinine levels compared to baseline in either the antibiotic or placebo group. One case of irreversible nephrotoxicity, defined as increasing uraemia which led to death, occurred in the gentamicin group. No further details about this individual were given.

Giri *et al* (34) was one of only two randomised studies published in the last 16 years. AKI, defined as a sudden (within 48 hours) decrease in renal function using Acute Kidney Injury Network Staging (53), was reported in both groups. All patients with AKI had a normal serum creatinine at one month follow up, without any further intervention. In non-randomised studies by Craig *et al* (50), Bailey *et al* (41), Craxford *et al* (42), Cobussen *et al* (47), Ahmed *et al* (46) and Dubrovskaya *et al* (45) no significant difference in rates of AKI were reported between gentamicin and comparator arms. In the majority of cases reported by Bailey *et al* (41), Cobussen *et al* (47), Ahmed *et al* (46) and Dubrovskaya *et al* (45) renal function returned to normal by the end of the follow up period. Bailey *et al* (41) reported 24 (9.4%) episodes of AKI (54), of which 21 had resolved at seven days post-op. Two of the three

patients whose AKI persisted had a normal creatinine at 28 days and 32 days. The third patient was lost to follow up, but had a normal creatinine at 23 months. Cobussen *et al* (47) compared creatinine on and after admission, as well as between the gentamicin and control groups. After admission there was no difference in the incidence and severity of AKI between the gentamicin and control groups. At 8-14 days after admission most patients returned to their baseline creatinine. Ahmed *et al* (46) reported that of those who developed AKI (55) post-operatively, 80% of those in the gentamicin group and 79% in the cefuroxime group had resolution prior to discharge. Dubrovskaya *et al* (45) reported that 76.9% of patients with nephrotoxicity (54) in the gentamicin group and 82.6% in the control group had a creatinine within normal limits at the time of discharge, p = 0.703. Sprowson *et al* (39) found that many of their participants had a transient rise in creatinine but in their analysis the authors only included participants with acute renal failure requiring High Dependency Unit (HDU) admission. Although the numbers were small in both groups, there was a significant difference in the frequency of HDU admission between patients who received gentamicin (0.33%) and those who received cefuroxime (0.07%) - p = <0.01. The authors speculated that the threshold for admission to HDU may have been lower in the more recent years when gentamicin was used, (October 2007 – February 2009), compared to the comparator group who received cefuroxime from May 2002 – September 2007.

Studies including Nielson *et al* (37), Mukherjee *et al* (38), Ross *et al* (51), Sprowson *et al* (39), Bell *et al* (40), Craxford *et al* (43), Nielson *et al* (44) and Walker *et al* (48) found significant differences between groups receiving single dose gentamicin and those who did not. Nielson *et al* (37), Mukherjee *et al* (38) and Nielson *et al* (44) analysed creatinine between 24-72 hours post-operatively and Ross *et al* (51) performed their evaluation immediately post-operatively. None of these studies provided data beyond four days after

treatment. Both studies by Nielson *et al* (37, 44) reported no statistically significant difference in the frequency of post-operative dialysis and in one (44) there was no difference in the median maximum serum creatinine after 72 hours.

Bell *et al* (40) was the largest cohort study identified and assessed the risk of AKI in patients receiving antibiotic prophylaxis before surgery, across five different surgical specialities. Unfortunately data and publication errors in the descriptive data tables, make it difficult to interpret the original data. The study reports an increase in rates of AKI in patients receiving gentamicin who underwent orthopaedic surgery, with the majority of AKI being transient Stage 1 (56). There was no association between AKI and gentamicin in urology, vascular, gastrointestinal or gynaecology surgical patients. The same NHS Trust also published Walker *et al* (48), the second largest cohort study. This assessed post-operative AKI in patients who had neck of femur (NOF) repair operations or other orthopaedic surgery. For this review we included only data provided for patients undergoing orthopaedic surgery other than NOF repair, as only this group received a single dose of gentamicin. The majority (83%) of AKI seen in both treatment groups was Stage 1 (56), with 9.86% reported in the gentamicin group and 8.03% in the co-amoxiclav comparison group. Similar small differences were also seen in rates of Stage 2 and 3 AKI. There is no comment on whether these differences were statistically significant but the authors suggest that changes in practice, such as anaesthetic technique and post-operative care may have contributed to the differences seen.

Craxford *et al* (43) found a statistically significant increase in AKI (54) between elective lower limb arthroplasty patients who received gentamicin plus flucloxacillin, compared to those who received cefuroxime (p = <0.01) but there was no significant difference in the frequency of haemofiltration between the groups. The difference in rates of AKI appeared to

be independent of potential confounders and was not seen in a subgroup analysis of patients undergoing different surgical procedures. AKI was commoner in the Total Knee Replacement (TKR) group, but not in the Total Hip Replacement (THR) group which might be related to the use of a pneumatic tourniquet in the TKR group.

Subgroup analysis

In studies where all participants were <75years of age there were no reported episodes of nephrotoxicity or rise in creatinine. In studies where a fixed dose of ≤240mg of gentamicin was given, four out of fourteen studies reported higher frequency of nephrotoxicity or a rise in creatinine in the gentamicin group. Of the 11 randomised controlled trials only one study reported nephrotoxicity in the gentamicin arm and this was not statistically significant. Twenty studies used gentamicin as a surgical prophylaxis, of which 17 reported either nephrotoxicity or a rise in creatinine in the gentamicin arm. This compares to one study out of the 16 that used gentamicin for another indication.

No meta-analysis was undertaken due to heterogeneity of the studies in relation to wide variations in patient demographics, co-morbidities, doses of gentamicin, study design and reporting of adverse events.

Table 2: Table of Adverse Events Data

Study (Year of publication)	Number of adverse events in all study arms	Comparator Arm	Frequency of adverse events in comparator group	Type of adverse event reported in comparator group	Adjunctive antibiotics in Gentamicin group	Frequency of adverse events in gentamicin group	Type of adverse event reported in gentamicin group
Adelman *et al* (1982)	0	Tobramycin	0/10	N/A	Nil	0/10	N/A
Ahmed *et al* (2016)	303 Some patients had >1 event	Cefuroxime	117/744	Post-op Acute kidney injury (63) Thirty day mortality (54)	Flucloxacillin	186/756	Post-op Acute kidney injury (125) Thirty day mortality (61)
Bailey *et al* (2014)	28	Cefuroxime	4/238	Acute kidney injury by RIFLE† R = (4)	Flucloxacillin	24/254	Acute kidney injury by RIFLE† R = (12) I = (7) F = (5)
Bell *et al* (2014)	1370	Cefuroxime or Coamoxiclav	548*	Acute kidney injury (548)	Flucloxacillin and/or Metronidazole	822*	Acute kidney injury (822)
Challagundla *et al* (2013)	48	Cefuroxime	11/100	Acute kidney injury by RIFLE R = (10) I = (1)	Flucloxacillin (High or Low dose)	37/98	Acute kidney injury by RIFLE R = (22) I = (8) F = (7)
Cobussen *et al* (2016)	41	Broad spectrum ß-lactam antibiotic or fluoroquinolones	21/123	Acute kidney injury by RIFLE R = (3) I = (1) F = (0) 28-day mortality (17)	Broad spectrum ß-lactam antibiotic	36/179	Acute kidney injury by RIFLE R = (4) I = (5) F = (3) 28-day mortality (24)
Contrepois *et al* (1985)	0	Dibekacin or tobramycin or netilmicin or amikacin	0/24	N/A	Nil	0/6	N/A
Craig *et al* (2012)	13	Cefuroxime	5/100	Reversible acute kidney injury (1) Not reversible acute kidney injury (4)	Co-Amoxiclav	8/100	Reversible acute kidney injury (5) Not reversible acute kidney injury (3)
Craxford *et al* (2014)	18	Cefuroxime	2/200	Acute kidney injury by RIFLE R = (2)	Flucloxacillin	16/200	Acute kidney injury by RIFLE R = (9) I + F = (7)
Craxford *et al* (2014)	Not available	Cefuroxime	Not available	No significant difference in acute kidney injury rates (p = 0.053)	Flucloxacillin	Not available	No significant difference in acute kidney injury rates (p = 0.053)
Creasey *et al* (1984)	9	Aztreonam + cephradine or clindamycin or metronidazole or naficillin	8/36	Transient taste disturbance, transient rise in serum glutamic pyruvic transaminase, transient rise in serum creatine phosphokinase	Aztreonam	1/12	Transient rise in glutamic pyruvic transaminase
Dobbs *et al* (1976)	0	Tobramycin	0/6	N/A	Nil	0/6	N/A
Dubrovskaya *et al* (2015)	85	Cefazolin	46/2587	Acute kidney injury by RIFLE R = (33) I = (10) F = (3)	Cefazolin or clindamycin or vancomycin	39/1590	Acute kidney injury by RIFLE R = (26) I = (12) F = (1)
Fried *et al* (1996)	17	Oral antibiotic based on urine culture sensitivity.	10/70	Fever, haematuria, dysuria	Nil	7/72	Fever, haematuria, dysuria
Giri *et al*	20	Amikacin +	8/50	Acute kidney injury Stage 1 (8)	Metronidazole	12/50	Acute kidney injury Stage 1 (10)

N/A – Not Applicable. * Denominator varies or is unclear. † RIFLE criteria (Risk Injury Failure Loss End-stage kidney disease).

(2016)		Metronidazole					Acute kidney injury Stage 2 (2)
Hira *et al* (1985)	0	Kanamycin	0*	N/A	Nil	0*	N/A
Jahre *et al* (1978)	0	Netilmicin	0/6	N/A	Nil	0/6	N/A
Jettoo *et al* (2013)	49	Cefuroxime	33/113	180 day mortality (33)	Amoxicillin	16/107	180 day mortality (16)
Kircaldy *et al* (2014)	306 Some patients had >1 event	Gemifloxacin + azithromycin	167/199 Some patients had >1 event	Nausea (74), Vomiting (10), Abdo pain (21), Diarrhoea (46), Fatigue (6), Dizziness (7), Tendon disorder (3)	Azithromycin	139/202 Some patients had >1 event	Nausea (56), Vomiting (15), Abdo pain (15), Diarrhoea (39), Fatigue (4), Dizziness (7), Injection site pain (2), tendon disorder (1)
Kleinschmidt *et al* (1983)	4	Amoxicillin	4/31	Nausea (mild to significant)	Nil	0/34	N/A
Lorber *et al* (2013)	0	Ofloxacin or Ciprofloxacin	0/581	N/A	Ofloxacin or Ciprofloxacin	0/1085	N/A
McEntee *et al* (1987)	0	No treatment	0/44	N/A	Nil	0/17	N/A
Meyers *et al* (1972)	0	Tobramycin	0/20	N/A	Nil	0/16	N/A
Mukherjee *et al* (2013)	24	Not available	Not available	Not available	Not available	24/40	Nephrotoxicity (24)
Ndele	7 Some patients had >1 event	Netilmicin	3/6 Some patients had >1 event	Transient earthy taste (2) Transient smell of alcohol (2) Light headedness 5-10mins (3)	Nil	0/6	N/A
Nielson *et al* (2013) ***Frequencies extrapolated from available published data***	865	Teicoplanin and Dicloxacillin	340/1307	Acute kidney injury (297) Postoperative dialysis (43)	Teicoplanin and Dicloxacillin	525/1716	Acute kidney injury (465) Postoperative dialysis (60)
Nielson *et al* (2014)	288 Some patients had >1 event	Teicoplanin and Dicloxacillin	126/668	Acute kidney injury (110) 1 year mortality (16)	Teicoplanin and Dicloxacillin	162/668	Acute kidney injury (145) 1 year mortality (17)
Pareek *et al* (1981)	0	Spectinomycin	0/20	N/A	Nil	0/20	N/A
Pons *et al* (1993)	6	Ceftizoxime	0/422	N/A	Vancomycin	6/404	Clinically significant hypotension and/or flushing ('red man syndrome')
Rakovec *et al* (1985)	38	No treatment	Not available	Not available	Metronidazole	38/572	Transient elevation of creatinine (19), short-lived increase SGOT+SGPT (13), eosinophilia (2), exanthema (4)
Ross *et al* (2013)	11	Cefuroxime	2/124	Acute kidney injury by RIFLE R = (2)	Flucloxacillin	9/149	Acute kidney injury by RIFLE R = (4) I = (3) F = (2)
Rowlands *et al* (1982)	0	Placebo	0/62	N/A	Clindamycin	0/67	N/A
Solgaard *et al* (2000)	21	No treatment	4/76	Reversible nephrotoxicity (4)	Dicloxacillin	17/87	Irreversible nephrotoxicity (1) Reversible nephrotoxicity (16)
Sprowson *et al* (2013)	11	Cefuroxime + gentamicin loaded cement	4/6094	Acute renal failure requiring High Dependency Unit (4)	Gentamicin loaded cement	7/2101	Acute renal failure requiring High Dependency Unit (7)
Sundman *et al* (1997)	4-5	Cefotaxime + norfloxacin	4 or 5/47 (inc 2 or 3 deaths)	Not available	Norfloxacin	0/54	N/A
Walker *et al*	1031	Co-amoxiclav	273/2975	Acute kidney injury Stage 1 (239)	Flucloxacillin	758/6267	Acute kidney injury Stage 1 (618)

N/A – Not Applicable. * Denominator varies or is unclear. † RIFLE criteria (Risk Injury Failure Loss End-stage kidney disease).

(2016)				Acute kidney injury Stage 2 (22) Acute kidney injury Stage 3 (12)			Acute kidney injury Stage 2 (95) Acute kidney injury Stage 3 (45)

N/A – Not Applicable. * Denominator varies or is unclear. † RIFLE criteria (Risk Injury Failure Loss End-stage kidney disease).

Discussion

Our systematic review suggests that single dose gentamicin can have an effect on renal function, but this is usually mild and/or transient. Of the 36 studies identified, there were 2599 episodes of creatinine rise or nephrotoxicity in the gentamicin group. However many cases resolved within a few days or weeks or occurred in populations with renal risk factors. No cases of ototoxicity were reported.

Our findings are in keeping with existing knowledge of gentamicin and its side effects, which is based on multiple dosing regimens. Nephrotoxicity is considered to be dose related.(57) Re-uptake of the drug occurs in the proximal renal tubule where it leads to high drug concentrations within the tubule cells.(58) The risk of nephrotoxicity can be minimised by serum-level monitoring with dose adjustment, and shortening the duration of treatment.(59) Several risk factors are thought to predispose to nephrotoxicity including increasing age, pre-existing renal disease, use of diuretics, exposure to radiographic contrast, circulating volume depletion and use of other nephrotoxic medication including ACE inhibitors, Non-steroidal anti-inflammatory drugs (NSAIDs), amphotericin or cisplatin.(11, 60-62) In multiple dosing of gentamicin the frequency of related nephrotoxicity is reported to be 10-25%.(63-65)

Although no episodes of ototoxicity were reported in our review Gentamicin is primarily vestibulotoxic(66). Causing damage to the vestibular apparatus, initially affecting the cristae and progressing to the striolar regions of the maculi(67). Clinically this leads to dizziness, ataxia and nystagmus. Destruction of the auditory sensory cells of the organ of Corti leads to cochleotoxicity which is associated with over-production of oxidative free radicals(68) and can present as hearing loss or tinnitus. In our review Kirkcaldy et al(5) was the only study to report seven episodes of dizziness in the gentamicin group, but an equal number of episodes

were reported in the comparator group. The ototoxicity of aminoglycosides, which is irreversible, does not correlate with drug levels in the fluid of the inner ear, drug dose or gentamicin serum concentration.(69, 70) In a study of 30 patients with gentamicin associated vestibulotoxicity, 16 had received less than the recommended maximum dose of 5mg/kg/day over 10 days.(70) A review of aminoglycoside toxicity including papers published between 1975 and 1982 identified 8 studies (559 patients) that evaluated gentamicin(71) and found the frequency of vestibulotoxicity to be 2.7%, and of cochlear toxicity 8.3%(71). A subsequent review in 2008, using different inclusion criteria, assessed 4 additional studies (147 patients) and found a frequency of vestibulotoxicity of 10.9% one week after completing treatment.(72) This review did not comment on cochlear toxicity and neither review assessed the effect of duration of therapy on risk of ototoxicity. In a case series of 33 patients with permanent gentamicin-induced vestibulotoxicity, 1 patient had developed vestibular toxicity after 5 days of treatment; all other patients had received a longer course of gentamicin.(73) In a larger case series, 6 of 103 patients presenting to a balance disorder clinic with a diagnosis of severe, symmetrical, selective, bilateral vestibular loss, had received only a single dose of gentamicin.(72) The lack of correlation between drug dose or serum concentration in causing vestibular or cochlear toxicity makes it difficult to predict which patients will be affected. Increasing age(74) and a mitochondrial DNA mutation, (m.1555A>G),(75, 76) have both been shown to increase a patient's susceptibility to cochleotoxicity, but not vestibulotoxicity.

The main strength of this systematic review was a robust search strategy and adherence to established protocols published by the Cochrane group (12) and Centre for Reviews and Dissemination at University of York.(77) This minimised the risk of excluding a potentially relevant study. Limiting the analysis to studies which had a comparator group provided a more robust evaluation of the adverse effects that were associated with gentamicin.

Many of the limitations of this review are in part due to the design or reporting of included studies. It would have been preferable to have reported a meta-analysis, but heterogeneity of the studies meant this would have been inappropriate. In patients receiving multiple interventions it can be difficult to identify the relative contribution of a single agent to reported adverse effects. In particular other factors such as concomitant medication, pre-existing co-morbidities and surgical procedures can affect the risk of kidney injury. In our review the studies (39-41, 43, 46, 48) that reported a statistically significant increase in AKI were all carried out in patients undergoing orthopaedic surgery. It is likely that patients are more vulnerable to the renal effects of gentamicin if they are older or are taking NSAIDs for joint pain.

Cohort studies contributed the largest proportion of data to the review with an associated risk of unidentified confounding factors leading to bias. The majority of studies used antibiotic combination regimens, again making it difficult to identify the specific role of gentamicin. Flucloxacillin alone is not a common cause of nephrotoxicity, but Challagundlla *et al* (36) reported a difference in AKI between high and low dose flucloxacillin groups when all other confounders were accounted for. Whether flucloxacillin has a synergistic effect to cause gentamicin toxicity is unclear, but studies with adjunctive antibiotics need to be interpreted with caution. Only one study (39) published after 1996 did not use an adjunctive antibiotic in combination with gentamicin.

The quality of studies was generally poor, specifically in defining and reporting adverse events, and especially for studies reporting prior to 2012. The risk of bias was therefore high or uncertain for many studies. Reporting of adverse events was often limited to one or two

sentences commenting on a lack of side effects. This limited data on adverse events also makes it difficult to identify specific subgroups that might be at higher risk of toxicity. Poor reporting of adverse events is a common problem even in otherwise high quality trials (19, 20). We were also unable to obtain 47 (5%) of the 933 potentially relevant reports. The majority (n=38) of these were conference abstracts, proceedings, dissertations or theses. Thirty of these 47 records also lacked a published abstract.

A relatively new indication for gentamicin is for the treatment of gonorrhoea. Gonorrhoea has been increasing in men and women in England since 2010, with a 21% increase between 2014-15(78). Multi drug resistance is common and an outbreak of highly level resistance to azithromycin was recently reported in England (79). The World Health Organisation (WHO) has listed *Neisseria gonorrhoeae* as a high priority pathogen for research and development of new antibiotics(80). Two systematic reviews have showed that single dose gentamicin is an effective treatment (4, 6) and this has been supported by a large clinical trial(5). This systematic review supports the use of single dose gentamicin as a safe alternative treatment for gonorrhoea.

Previous reports have found that repeated single daily dosing of aminoglycosides has an equivalent or lower level of toxicity compared to multiple daily doses (11). Other anti-microbials have also shown an improved side effect profile when used as single dose daily therapy(81) but our review is the first to assess the toxicity of a single, one-off, dose of gentamicin.

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